REMARKS

Claims 1-10, 12-16, 21, 22, 26-32, 50-97, and 101-119 are pending in the application, new claim 119 having been added by the above amendment. Claims 1, 12, 31, 102, and 112 are amended to delete "or derivative thereof". The description of particle size in several claims is revised as requested by the examiner, without altering the scope of this element. Claims 12 and 112 are amended to recite a limitation that also appears in claims 1 and 102, from which claims 12 and 112 respectively depend. Thus, these amendments do not alter the scope of claims 12 and 112. Claim 102 is amended to specify that the composition consists of (A) a polypeptide; (B) one or more surfactant compounds, and (C) one or more additives selected from a defined group. Support for this amendment can be found, for example, at pages 14-15, carryover sentence. Claim 103 is amended to make it consistent with these amendments to claim 102, from which it depends. New claim 119 derives support, for example, from page 15, lines 1-7. All other amendments are to correct typographical or grammatical errors. No new matter has been added.

Claims 2, 21, 22, 26-30, 32, 50-97, and 103 have been withdrawn from consideration by the Examiner because these claims are directed to unelected restriction groups. Applicants reiterate their intention to rejoin these unelected restriction groups upon the Examiner's determination that the claims under consideration are allowable, in accordance with the procedure set forth by the Examiner in his Restriction Requirement mailed December 30, 1999.

All of the claims are rejected on various grounds, discussed below.

Obviousness-type double patenting

Claims 1 and 102 were provisionally rejected for obviousness-type double patenting over claim 42 of copending application Serial No. 08/960,093. To obviate this rejection, Applicants submit herewith a terminal disclaimer signed on behalf of the assignee of the present application and of Serial No. 08/960,093. Withdrawal of the rejection is respectfully requested.

35 USC 112, first paragraph

Claims 1, 3-10, 12-16, 31, 101, 102, and 104-118 were rejected as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner states that the language added to claim 1 specifying that each chain of the double-chain phospholipid is 8 or fewer carbon atoms in length is "new matter" in that it excludes double-chain phospholipids in which the fatty acid portion consists of nine carbon atoms. Applicants traverse this rejection. Table I on page 22 of the specification teaches that dioctanoylphosphatidylcholine (with two 8-carbon chains) was an effective enhancer, while didecanoylphosphatidylcholine (with two 10-carbon chains) was not. The original text of the specification further teaches at page 11, lines 26-31, that double-chain phospholipids of shorter chain length are expected to be useful enhancers. (Note that this original text was amended in the response (filed January 12, 2001) to the previous Office Action mailed July 14, 2000, in order to correct a discrepancy between the description at page 11 and the data provided in Table I; however, the statement at issue was not altered.) Given the fact that eight carbons was the longest double-chain phospholipid chain length found to be effective in the reported experiments, and the fact that lipid chains of phospholipids are generally multiples of 2-carbon units (thereby excluding any 9-carbon chains), Applicants maintain that the specification adequately supports the limitation "eight or fewer carbon atoms in length." An amendment adding this limitation has been accepted in a number of related applications filed by Applicants based on the same or similar disclosure: see, for example, the Reexamination Certificate issued February 13, 2001, for U.S. Patent No. 5,518,998 C1. Withdrawal of the rejection is therefore requested.

35 USC 112, second paragraph

Claims 1, 3-10, 12-16, 31, 101, 102, and 104-118 were rejected as allegedly indefinite for reciting "less than about" 10 microns. While not acquiescing in the rejection, Applicants have amended the relevant claims as requested by the Examiner, thereby rendering the rejection moot. The amendment does not change the scope of the amended claims.

35 USC 102(b) and (e)

Claims 1, 3-10, 12, 101-112, and 117 were rejected as anticipated under 35 USC 102(b) by Wang (US Patent No. 5,011,678), based on the Examiner's interpretation of Wang's STDHF steroid as being a "bile salt derivative". Without acquiescing in this ground for rejection, Applicants have amended the relevant claims to omit reference to bile salt derivatives. Withdrawal of the rejection is therefore respectfully requested.

Claims 12, 102, 104-111, and 118 were rejected as anticipated under 35 USC 102(e) by Illum (US Patent No. 5,707,644). With regard to claim 12, the Examiner states that the claim permits phospholipids "of any constitution." This ignores the basic patent law tenet that requires any dependent claim to be interpreted as including all the limitations of a claim from which it depends. (See 35 USC 112, paragraph four: "A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.") Because claim 12 depends from claim 1, claim 12 includes all of the limitations of claim 1, including any restrictions on the identity of the phospholipid set forth in the latter claim. In order to remove this as an issue in the Examiner's mind, however, Applicants have amended claim 12 to repeat the phospholipid description set forth in claim 1. This amendment obviously does not change the scope of claim 12. Withdrawal of the rejection is respectfully requested.

With regard to claim 102 and its dependent claims, the Examiner notes that both Illum and the instant specification state that starch can be included as an ingredient. Without acquiescing in this ground for rejection, Applicants have amended claim 102 to limit the claimed composition to one that consists of (A) a polypeptide, (B) a surfactant, and (C) one or more additives selected from a defined list that does not include starch. Withdrawal of the rejection is therefore respectfully requested.

Claims 12 and 112 were rejected under 35 USC 102(b) as anticipated by Durani (WO 91/16882), again because of the Examiner's belief that the limitations regarding the phospholipid that appear in claims 1 and 102 may not apply to their dependent claims 12 and 112. Applicants again seek to reassure the Examiner that these limitations do indeed carry over into the dependent claims, by operation of patent law; however, to remove this as an issue, both claims 12 and 112 have been amended to repeat the phospholipid description of claims 1 and 102. Withdrawal of the rejection is respectfully requested.

Sekine (JP 632932)

At page 6 of the Office Action, the Examiner invites Applicants to "comment on the validity of a rejection of claims 2 and 103 over Sekine (JP 632932)," which the Examiner characterizes as teaching a particle size of 10-250 microns. According to the Examiner,

> Claims 2 and 103 permit particles with a diameter of greater than 10 microns. Although claims 2 and 103 require the presence of 10 micron particles there is no lower limit to the percent of the total particles that must be 10 microns or less. Thus, claims 2 and 103 would encompass compositions in which 99.99% of the particles are greater than 10 microns.

Applicants respectfully point out that each of claims 1 and 102, from which claims 2 and 103 respectively depend, requires that at least 50% of the total mass of polypeptide and surfactant consist of primary particles having a diameter less than 10 microns or equal to about 10 microns. This limitation of course applies to every claim that depends from claim 1 or 102. Claims 2 and 103 further specify that the additive of (C) can be made up of larger "coarse" particles. Thus, although the Examiner is correct in saying that claims 2 and 103 encompass compositions in which 99.99% of the particles are of a size greater than 10 microns, this would be true only where the large particles that make up at least 99.98% of the total composition are made up of the additive specified by part (C) of claims 1 and 102, and not the active ingredients specified in parts (A) and (B). This embodiment would leave at most only 0.02% of the particles being made up of polypeptide and surfactant. Sekine teaches a composition for trans-nasal administration, in which all of the components are supposed to end up in the nose, not the lungs. (See pages 14-15 of the Sekine translation supplied by the Examiner.) According to Sekine, this is accomplished by ensuring that the components that are supposed to be delivered to the nasal mucosa have a particle size greater than 10 microns. Thus, Sekine teaches away from making a composition in which at least 50% of the total mass of active ingredients (polypeptide and enhancer) consists of small particles that are likely to bypass the intranasal surfaces and enter the lung, i.e., particles having a diameter less than 10 microns or equal to about 10 microns. Furthermore, Sekine

teaches away from compositions that do not contain a hygroscopic ("water-absorbing") component (a component that apparently improves absorption across the nasal mucosa). Neither claims 1 and 2 (which specify that the only additives that can be present are "non-hygroscopic" ones), nor claims 102 and 103 (which, as amended, specify an additive selected from a particular list) cover compositions comparable to those taught by Sekine. Thus, Sekine is relevant to the present claims only as a teaching-away. A rejection based upon Sekine would not be warranted.

IDS Issues

On page 6 of the Office Action, the Examiner states that certain references were stricken from the Information Disclosure Statement because either no translation was provided or the reference was not received. Applicants submitted a new Information Disclosure Statement on May 23, 2001, enclosing (among other things) English translations of Japanese patents Hei 4-149126 and Hei 4-41421. These correspond to two of the Japanese patents stricken by the Examiner from the Forms 1449 originally filed on July 18, 2000 (reference AL) and July 5, 2000 (reference AM). Enclosed herewith is a new Form 1449 listing the English abstract of the third Japanese patent, JP 1117825, as document AQ in the category "Other Documents", as requested by the Examiner. Also listed are AR: Köhler et al., "Nicht radioaktives Verfahren zur Messung der Lungenpermeabilität: Inhalation von Insulin", Atemw. Lungenkrkh., Jahrgang 13, Nr. 6/1987, S. 230-232, with Abstract in English and AS: Köhler et al., "Aerosols for Systemic Treatment", Lung, Suppl. 677-684, 1990. According to the Examiner, the first Köhler et al. reference was stricken because no translation was provided, and the second Köhler et al. reference was stricken because it was not received. Applicants enclose a copy of each, and note that, although the AR reference is largely in German, it does have an English abstract at the bottom of column 1 of page 230.

The Examiner is respectfully requested to initial each reference submitted herewith and on May 23, 2001, and to confirm that the enclosed references and those submitted on May 23, 2001, satisfy the Information Disclosure Statement concerns raised in the Office Action.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a $18 check for excess claim fees and a $920 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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Version with markings to show changes made

In the claims:

Claims 1, 2, 12, 21, 31, 61, 78, 79, 96, 102, 103, 112 and 117 have been amended as follows:

1. (Amended) A propellant-free composition consisting of (A) a polypeptide, (B) one or more surfactant compounds which (i) have a consistency that permits them to be processed into primary particles having a diameter less than 10 microns, and (ii) enhance the systemic absorption of said polypeptide in the lower respiratory tract of a patient, and (C) optionally one or more non-hygroscopic additives, said composition being in the form of a dry powder suitable for inhalation from a dry powder inhaler device, wherein at least 50% of the total mass of (A) and (B) consists of primary particles having a diameter less than 10 microns or equal to about 10 microns, and wherein each of the one or more surfactant compounds is selected from the group consisting of a salt of a fatty acid, bile salt [or derivative thereof], single-chain phospholipid, double-chain phospholipid in which each chain of the double-chain phospholipid is eight or fewer carbon atoms in length, alkyl glycoside, cyclodextrin or derivative thereof, salt of a glycyrrhizine acid, salt of a saponin glycoside, salt of an acyl carnitine, and sodium salicylate.

2. (Amended) A composition as claimed in claim 1, including said one or more non-hygroscopic additives, said one or more non-hygroscopic additives comprising a carrier that comprises either

(a) particles having a diameter of less than 10 microns or equal to about 10 microns, such that at least 50% of said composition consists of primary particles having a diameter of less than 10 microns or equal to about 10 microns; or

(b) coarse particles having a diameter of at least 20 microns, such that an ordered mixture is formed between (i) the carrier and (ii) the polypeptide of (A) and the one or more surfactant compounds of (B).

12. (Amended) The composition of claim 1, wherein at least one of said one or more surfactant compounds is a bile salt [or derivative thereof], an alkyl glycoside, a cyclodextrin or derivative thereof, [or a phospholipid] a single-chain phospholipid, or a double-chain phospholipid in which each chain of the double-chain phospholipid is eight or fewer carbon atoms in length.

21. (Amended) A method for systemic administration of a biologically active polypeptide, comprising

providing a composition comprising a mixture of active compounds (A) a biologically active polypeptide, and (B) an enhancer compound which (i) has a consistency that permits it to be processed into primary particles having a diameter less than 10 microns, and (ii) enhances the systemic absorption of the polypeptide in the lower respiratory tract of a patient, said composition being in the form of a dry powder suitable for inhalation from a dry powder inhaler device; and

causing said patient to inhale through the mouth said composition from a dry powder inhaler device; provided that at least 50% of the total mass of the active compounds, at the point the active compounds enter the respiratory tract of the patient, consists of particles having a diameter less than 10 microns or equal to about 10 microns.

31. The composition of claim 1, wherein at least one of said one or more surfactant compounds is a bile salt [or derivative thereof].

61. (Amended) A composition[,] comprising a mixture of active compounds (A) a biologically active polypeptide, and (B) an enhancer compound [which] that (i) has a consistency that permits it to be processed into primary particles having a diameter less than 10 microns, and (ii) enhances the systemic absorption of said polypeptide in the lower respiratory tract of a patient, said composition being in the form of a dry powder suitable for inhalation from a dry powder inhaler device, wherein at least 50% of the total mass of active compounds consists of

primary particles having a diameter less than 10 microns or equal to about 10 microns, said primary particles optionally being formed into agglomerates; and

a carrier comprising particles having a diameter of at least 20 microns, such that an ordered mixture is formed between the active compounds and the carrier.

78. (Amended) A dry powder inhaler device containing a composition comprising a mixture of active compounds (A) a biologically active polypeptide, and (B) an enhancer compound which (i) has a consistency that permits it to be processed into primary particles having a diameter less than 10 microns, and (ii) enhances the systemic absorption of said polypeptide in the lower respiratory tract of a patient, said composition being in the form of a dry powder suitable for inhalation from a dry powder inhaler device, wherein at least 50% of the total mass of active compounds consists of primary particles having a diameter less than 10 microns or equal to about 10 microns, said primary particles optionally being formed into agglomerates; the dry powder inhaler device being adapted for inhalation through the mouth.

79. (Amended) The dry powder inhaler device of claim 78, wherein the composition comprises a carrier, which comprises either

(a) particles having a diameter of less than 10 microns or equal to about 10 microns, such that at least 50% of said composition consists of optionally agglomerated primary particles having a diameter of less than 10 microns or equal to about 10 microns; or

(b) particles having a diameter of at least 20 microns, such that an ordered mixture is formed between the active compounds and the carrier.

96. (Amended) The dry powder inhaler device of claim 78, wherein said composition is in the form of said agglomerates, said device being configured to induce the majority of said agglomerates to break down into particles having a diameter less than 10 microns or equal to about 10 microns, upon inhalation of said agglomerates from said device.

102. (Amended) A propellant-free composition [comprising] consisting of

(A) a polypeptide [and] ;

(B) a surfactant compound that (i) has a consistency that permits [them] it to be processed into primary particles having a diameter less than 10 microns, and (ii) enhances the systemic absorption of said polypeptide in the lower respiratory tract of a patient ; and,

(C) one or more additives selected from the group consisting of a mono- or disaccharide, raffinose, melezitose, sugar alcohol and polyol, said composition being in the form of a dry powder suitable for inhalation from a dry powder inhaler device and into the lower respiratory tract, wherein at least 50% of the total mass of (A) and (B) consists of primary particles having a diameter less than 10 microns or equal to about 10 microns, and wherein the surfactant compound is selected from the group consisting of a salt of a fatty acid, bile salt [or derivative thereof], single-chain phospholipid, double-chain phospholipid in which each chain of the double-chain phospholipid is eight or fewer carbon atoms in length, alkyl glycoside, cyclodextrin or derivative thereof, salt of a glycyrrhizine acid, salt of a saponin glycoside, salt of an acyl carnitine, and sodium salicylate.

103. (Amended) The composition of claim 102, [further comprising a non-hygroscopic additive comprising a carrier, which comprises] wherein the one or more additives comprise either

(a) particles having a diameter of less than 10 microns or equal to about 10 microns, such that at least 50% of the composition consists of primary particles having a diameter of less than 10 microns or equal to about 10 microns; or

(b) coarse particles having a diameter of at least 20 microns, such that an ordered mixture is formed between (i) the [carrier] one or more additives, and (ii) the polypeptide of (A) and the surfactant compound of (B).

112. (Amended) The composition of claim 102, wherein the surfactant compound is a bile salt [or derivative thereof], an alkyl glycoside, a cyclodextrin or derivative thereof, [or a phospholipid] a single-chain phospholipid, or a double-chain phospholipid in which each chain of the double-chain phospholipid is eight or fewer carbon atoms in length.

117. (Amended) The composition of claim 102, wherein the surfactant compound is a bile salt [or derivative thereof].